

AMENDMENT TO THE CLAIMS:

This listing of Claims will replace all prior versions of Claims in the application.

Listing of Claims:

1-36. (Canceled)

37. (New) A modified animal cell or a progeny thereof produced by a method comprising:

- (a) introducing a targeting DNA construct into a plurality of cells of an inbred strain of animal in vitro, wherein said targeting DNA construct comprises (i) a targeting DNA sequence isolated from said inbred strain of animal and (ii) at least one modification sequence, such that said targeting DNA sequence undergoes homologous recombination with a target DNA sequence in the genome of said cells and;
- (b) isolating a modified animal cell in which said target DNA sequence comprises said at least one modification sequence; and
- (c) incubating said modified animal cell.

38. (New) A modified animal cell or a progeny thereof, said modified animal cell comprising a modification sequence in a target DNA sequence in the genome of said cell, said modification sequence being flanked by a targeting DNA sequence that has undergone homologous recombination in vitro with said target DNA sequence, wherein said targeting DNA sequence and said modified animal cell are isolated from the same inbred strain of animal.

39. (New) A modified animal cell comprising a modification sequence in a target DNA sequence, said modification sequence being flanked by a targeting DNA sequence in genome of said cell, wherein said modified animal cell is isolated from a genetically modified animal produced by a method comprising

- (a) introducing a plurality of embryonic stem cells of an inbred strain of animal into a blastocyst, wherein said plurality of embryonic stem cells comprise said target DNA sequence modified in vitro by homologous recombination with a targeting DNA construct, said targeting DNA construct comprising (i) said modification sequence and (ii) said targeting DNA sequence that is isolated from the same inbred strain of animal as said embryonic stem cells; and
- (b) growing said blastocyst in a female animal to produce said genetically modified animal.

40. (New) The modified animal cell of claim 37, 38, or 39, wherein said animal is a non-murine animal, a non-human animal, a mammal, a vertebrate, or a mouse.

41. (New) The modified animal cell of claim 37, 38, or 39, wherein said modified animal cell is an embryonic stem cell, a germ cell, or a somatic cell.

42. (New) The modified animal cell of claim 41 wherein said somatic cells are hematopoietic cells, T-lymphocytes, epithelial cells, endothelial cells, adrenal medulla cells, keratinocytes, fibroblasts, osteoblasts, osteoclasts, neurons, ganglion cells, retinal cells, liver cells, myoblast cells, cells of the islets of Langerhans, or stem cells of the above somatic cells.

43. (New) The modified animal cell of claim 37, 38, or 39, wherein said target DNA sequence comprises a coding region, a promoter, an enhancer, a terminator, an intron, or an inter-genic region.

44. (New) The modified animal cell of claim 37, 38, or 39, wherein said targeting DNA sequence is at least about 75, 100, 150, 200, 300, 500, 1000, 2,500, 8,000 or 15,000 base pairs.

45. (New) The modified animal cell of claim 37, 38, or 39, wherein said targeting DNA sequence is at least 97%, 99.0%, 99%, 99.5%, 99.6, or 99.9% identical to said target DNA sequence.

46. (New) The modified animal cell of claim 37, 38, or 39, wherein said target DNA sequence and targeting DNA sequence comprises at least about 75, 150, or 500 base pairs in length that are 100% identical.

47. (New) The modified animal cell of claim 37, 38, or 39, wherein said targeting DNA sequence is derived from cells of the same individual animal or a sibling thereof as cells comprising said target DNA sequence.

48. (New) The modified animal cell of claim 37, 38, or 39, wherein said targeting DNA construct comprises a heterologous gene that is a selectable marker, an antibiotic resistance gene, a gene conferring the ability to grow on selected substrates, or a gene encoding proteins that produce detectable signals.

49. (New) The modified animal cell of claim 48 wherein said heterologous gene comprises a transcriptional start signal, a translational start signal, and/or a termination signal.

50. (New) The modified animal cell of claim 48 wherein said heterologous gene is a neomycin resistance gene, a hygromycin resistance gene, a thymidine kinase gene, a hypoxanthine phosphoribosyl transferase gene, or a guanine/xanthine phosphoribosyl transferase gene.

51. (New) The modified animal cell of claim 48 wherein said targeting DNA construct further comprises a second heterologous gene which is not incorporated into the genome of said cell following homologous recombination between said target DNA sequence and said targeting DNA sequence.

52. (New) The modified animal cell of claim 51 wherein said second heterologous gene is a Herpes Simplex Virus-thymidine kinase gene.

53. (New) The modified animal cell of claim 37, 38, or 39, wherein said modification sequence is flanked on both sides by said targeting DNA sequence.

54. (New) The modified animal cell of claim 49 wherein said transcriptional start signal comprises a metallothionein promoter, a thymidine kinase promoter, a beta-actin promoter, an immunoglobulin promoter, a SV40 promoter, or a human cytomegalovirus promoter.

55. (New) The modified animal cell of claim 37 or 39, wherein said introducing step comprises the use of microinjection, electroporation, transfection, calcium phosphate precipitation, liposomes, viral capsids, protoplast fusion, or ballistic penetration.

56. (New) The modified animal cell of claim 37 or 39, wherein said method further comprises selecting said modified animal cells.

57. (New) The modified animal cell of claim 37, wherein said method further comprises constructing said targeting DNA construct in which said modification sequence is flanked by a targeting DNA sequence.

58. (New) The modified animal cell of claim 37, 38, or 39, wherein said target DNA sequence in said modified animal cell is modified by an insertion of a sequence, a deletion of a sequence, a substitution of a sequence, or a combination thereof.

59. (New) The modified animal cell of claim 37, 38, or 39, wherein said modification sequence is identical to a segment of said target DNA sequence except a sequence that is to be deleted in said animal cell.

60. (New) The modified animal cell of claim 37, 38, or 39, wherein said modification sequence is a heterologous sequence relative to said target DNA in said genome of said cell.

61. (New) The modified animal cell of claim 58 wherein said deletion of a sequence comprises deletion of at least one exon, at least one intron, at least a non-coding region, or a combination thereof.

62. (New) The modified animal cell of claim 37, 38, or 39, wherein said modification sequence disrupts or enhances expression of a gene in said target DNA sequence.

63. (New) The modified animal cell of claim 37, 38, or 39, wherein said homologous recombination comprises a single crossover, a double crossover, or a gene conversion.

64. (New) The modified animal cell of claim 37, 38, or 39, wherein said animal is 129 strain of mouse or BALB/c strain of mouse.

65. (New) The modified animal cell of claim 37, 38, or 39, wherein said modification sequence comprises a gene encoding a polypeptide and wherein said modified animal cell produces said polypeptide.

66. (New) The modified animal cell of claim 37, 38, or 39, wherein said modification sequence corrects a defective gene in said target DNA.

67. (New) The modified animal cell of claim 39, wherein said genetically modified animal is non-chimeric and is produced by said method further comprising (c) breeding said genetically modified animal with a second animal to produce a genetically modified animal that is non-chimeric.

68. (New) The modified animal cell of claim 67 wherein said genetically modified animal and said second animal are members of the same strain.

69. (New) The modified animal cell of claim 67 wherein said genetically modified animal is a sibling of said second animal.

70. (New) The modified animal cell of claim 39, wherein said blastocyst is from a different parental strain than said embryonic stem cells.

71. (New) A non-human animal comprising cells that comprises a modification sequence in a target DNA sequence, said animal produced by a method comprising:

- (a) introducing a targeting DNA construct into embryonic stem cells of an inbred strain of animal in vitro, wherein said targeting DNA construct comprises at least one modification sequence and a targeting DNA sequence that is isolated from the same inbred strain of animal as said embryonic stem cells;
- (b) isolating a modified embryonic stem cell in which said target DNA sequence is modified in vitro by homologous recombination between said targeting DNA sequence and said target DNA sequence;
- (c) introducing said modified embryonic stem cell and progenies thereof into a blastocyst; and
- (d) growing said blastocyst in a female animal to produce said animal.

72. (New) The non-human animal of claim 71 wherein said method further comprises (e) breeding said animal of step (d) with a second animal to produce a non-chimeric animal.

73. (New) The non-human animal of claim 71 wherein said method further comprises (e) breeding said animal of step (d) with a second animal to produce a non-chimeric animal; and (f) breeding said non-chimeric animal with a third animal comprising said modification sequence in one allele of said target DNA sequence to produce a non-human animal comprising said modification sequence in both alleles of said gene.

74. (New) The non-human animal of claim 71, wherein said blastocyst is from a different parental strain than said embryonic stem cells.

75. (New) The non-human animal of claim 71, 72, or 73, wherein said animal is a non-murine animal, a mammal, a vertebrate, or a mouse.

76. (New) The non-human animal of claim 71, 72, or 73, wherein said modification sequence corrects a defective gene in said target DNA sequence.

77. (New) The non-human animal of claim 71, wherein said target DNA sequence comprises a coding region, a promoter, an enhancer, a terminator, an intron, or an inter-genic region.

78. (New) The non-human animal of claim 71, 72, or 73, wherein said targeting DNA sequence is at least about 75, 100, 150, 200, 300, 500, 1000, 2,500, 8,000 or 15,000 base pairs.

79. (New) The non-human animal of claim 71, 72, or 73, wherein said targeting DNA sequence is at least 97%, 99.0%, 99%, 99.5%, 99.6, or 99.9% identical to said target DNA sequence.

80. (New) The non-human animal of claim 71 wherein said target DNA sequence and targeting DNA sequence comprises at least about 75, 150, or 500 base pairs in length that are 100% identical.

81. (New) The non-human animal of claim 71 wherein said targeting DNA sequence is derived from cells of the same individual animal or a sibling thereof as cells comprising said target DNA sequence.

82. (New) The non-human animal of claim 71, 72, or 73, wherein said targeting DNA construct comprises a heterologous gene that is a selectable marker, an antibiotic resistance gene, a gene conferring the ability to grow on selected substrates, or a gene encoding proteins that produce detectable signals.

83. (New) The non-human animal of claim 82 wherein said targeting DNA construct further comprises a second heterologous gene which is not incorporated into the genome of said modified cell following homologous recombination between said target DNA sequence and said targeting DNA sequence.

84. (New) The non-human animal of claim 71, wherein said method further comprises selecting said modified animal cells.

85. (New) The non-human animal of claim 71, 72, or 73, wherein said target DNA sequence in said modified animal cell is modified by an insertion of a sequence, a deletion of a sequence, a substitution of a sequence, or a combination thereof.

86. (New) The non-human animal of claim 71, 72, or 73, wherein said homologous recombination comprises a single crossover, a double crossover, or a gene conversion.

87. (New) The non-human animal of claim 71, 72, or 73, wherein said inbred strain of animal is 129 strain of mouse or BALB/c strain of mouse.

88. (New) The non-human animal of claim 71, 72, or 73, wherein said modification sequence comprises a gene encoding a polypeptide and wherein said modified animal cell produces said polypeptide.